Multi-omics : are we looking in the wrong place ?

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Some ad-hoc thoughts on analysis

- The need to reduce dimension
- PCA/PCR, PLS, LASSO, Treelets, Signatures ?
- What do we mean by « sparse » ?
- Basis selection : linear transform, clustering, kernel transform, indexing.

The need to reduce dimension

- Whole genome methylation via chip : 450k sites : comparable to GWAS (but in GWAS, exclude rare variants)
- Via conversion and NGS : 27 million sites : comparable to whole exome sequancing (but regard only variable sites)
- GWAS still typically analysed site by site

Whole exome ?

- Too many rare variants… which are also too rare !
- Various aggregating schemes
- None really work except for highly tuned gene-specific techniques (via MAP, GVGD, SIFT)
- Big success is Mutation Signatures.

Mutation signatures

- Divide all mutations into 96 types
- Count up how many of each across the entire genome or exome
- Further reduce the dimension by Negative Matrix Factorisation (pick out un-correlated combinations)
- Characterises eg UV, Benzo-A-Pyrene, aristolochic acid, APOP-E mechanism.

Model Selection

- LASSO was going to be « the solution »
- Works very poorly for selecting correlated variables : doesn't take advantage of averaging to improve prediction (many of the problems fixable by modified versions)
- Computationally infeasible for WG
- Feature : ensures sparse models.

PCA, PCR, PLS

- Finds new basis that maximises variance per variable (or correlation)
- « No reason to suppose that the crucial information is not in the last component » - D. Cox
- Often criticised as « difficult to interpret » and « not sparse »
- If the a model with just first two PC's gave AUC=0.99, is it really not sparse ?

PCA uniqueness

- No real biological reason to suppose PCA basis will be adapted (except maybe the first PC)
- Independent processes might generate independent features, but PCA is uniquely determined by the maximum variance condition
- Infinite choice of orthogonal bases

Fourier/Wavelets/Treelets

- These are kernel transforms
- Do not map points to points, but patterns to points (and vice-versa)
- FT : time ↔ frequency
- Wavelets : nested packets of frequency bursts
- Treelets : attempt to extend wavelet ideas to un-ordered variables

Fourier example

- Imagine a toxin that caused every 15th base to be mutated
- Could be described by a single Fourier component
- Not describable by any reasonable LASSO, Ridge-regression, PCR, PLS etc model.
- Would you call it sparse ?

Fourier vs Index transform

- FT decomposes a genome-wide signal into superposition of frequencies
- Index transform transforms the original text to a list of locations of every pattern
- Or we could throw away the location and just keep the frequency of occurrence of each pattern
- This is first step of Mutation Signatures...

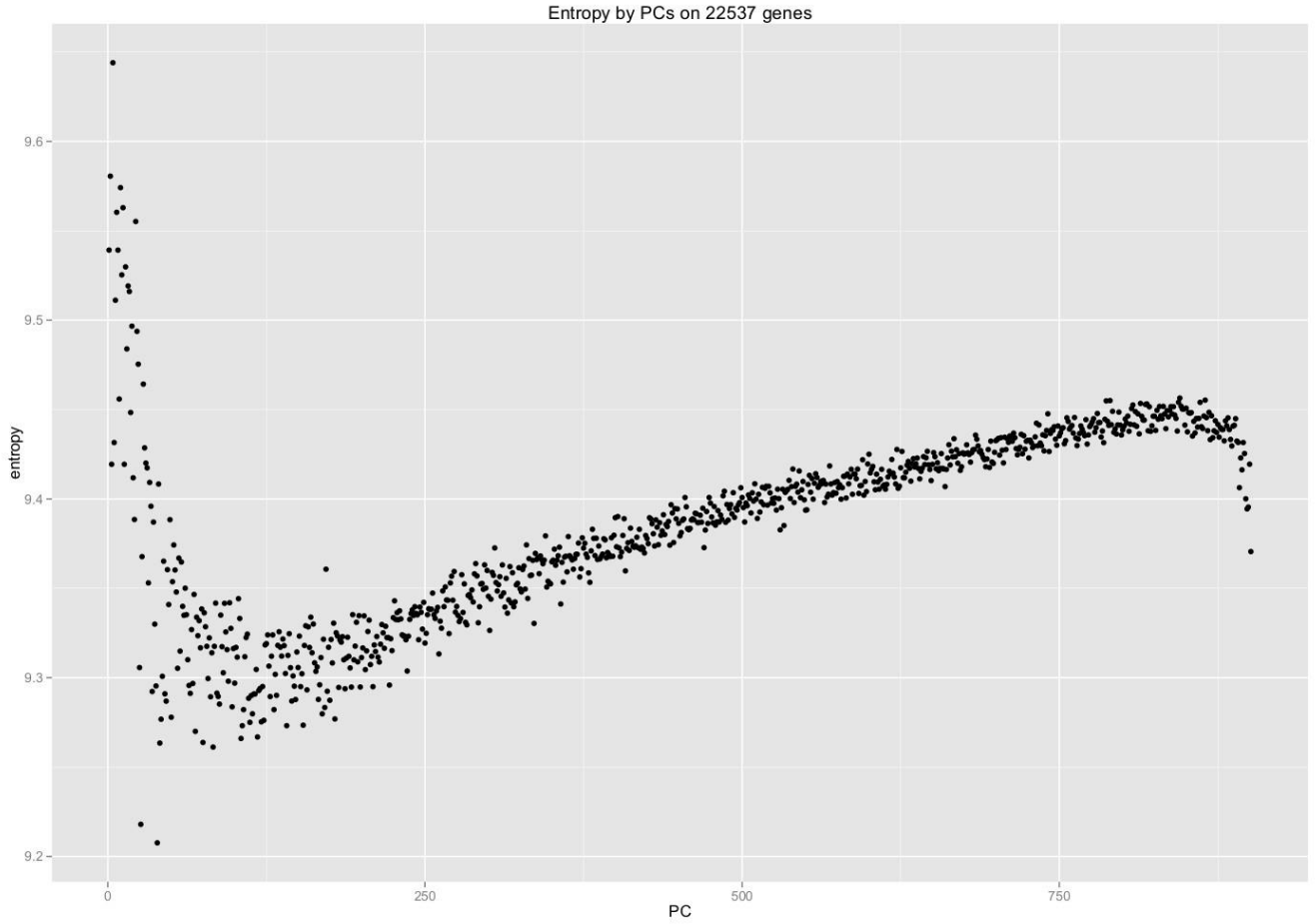
Index Transform example

- Imagine a toxin that causes A→T mutations, but only in context C(A→T)G
- Not a possible LASSO, PCR, etc model.
- Is it sparse ?
- (To make a complete transform we can add more context, ie 2, 3 or more bases 5' and 3')
- In fact IT is closest to WT.

Empirically...

- Can look to see what type of sparsity may be appropriate
- Use entropy of component loadings 22,537 genes
- Expect first PC will be close to uniform average, hence maximal entropy.
- Maximum possible Q=10.02, PC1 Q~9.65, min Q~9.25

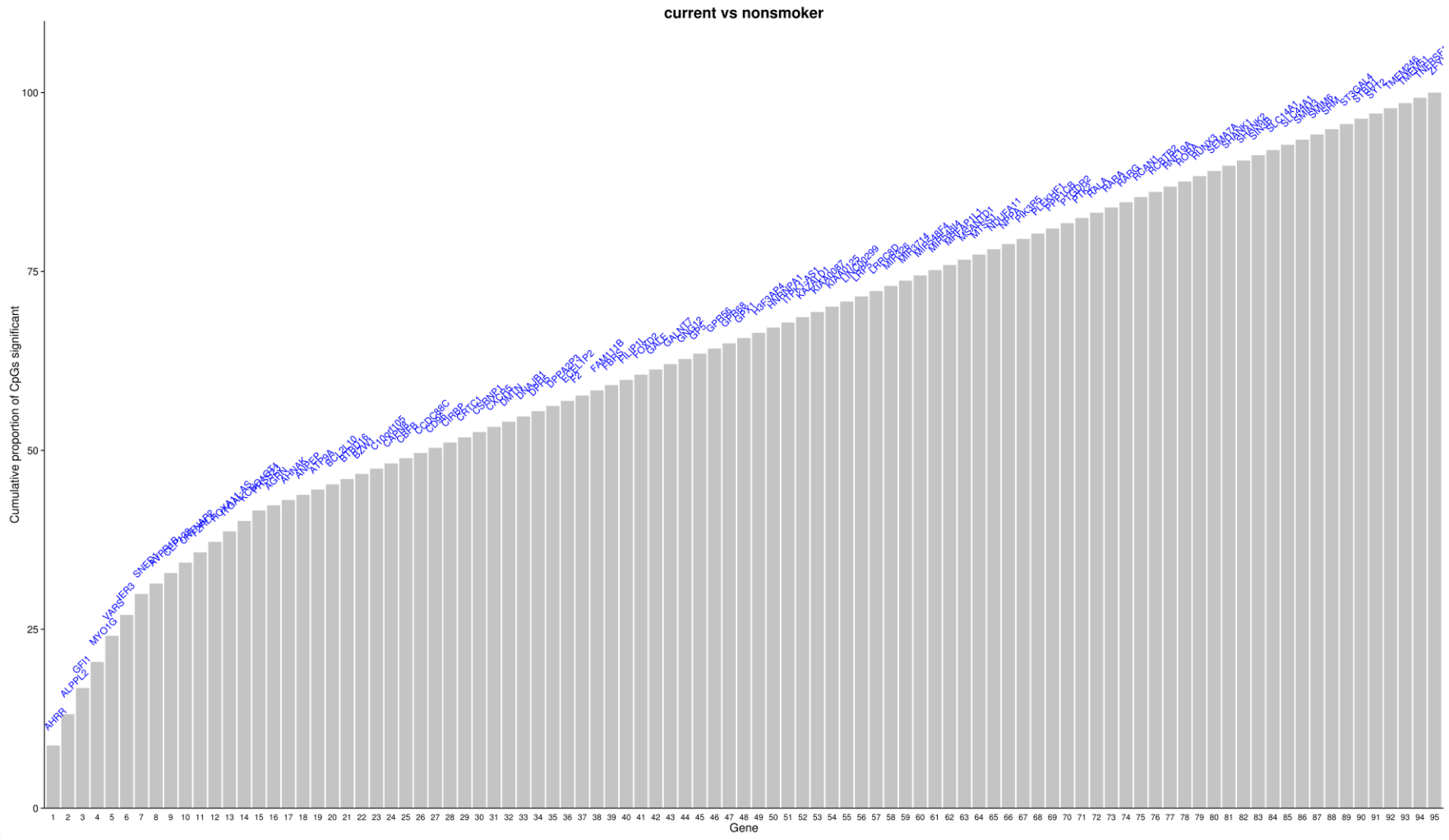
Entropy by PC



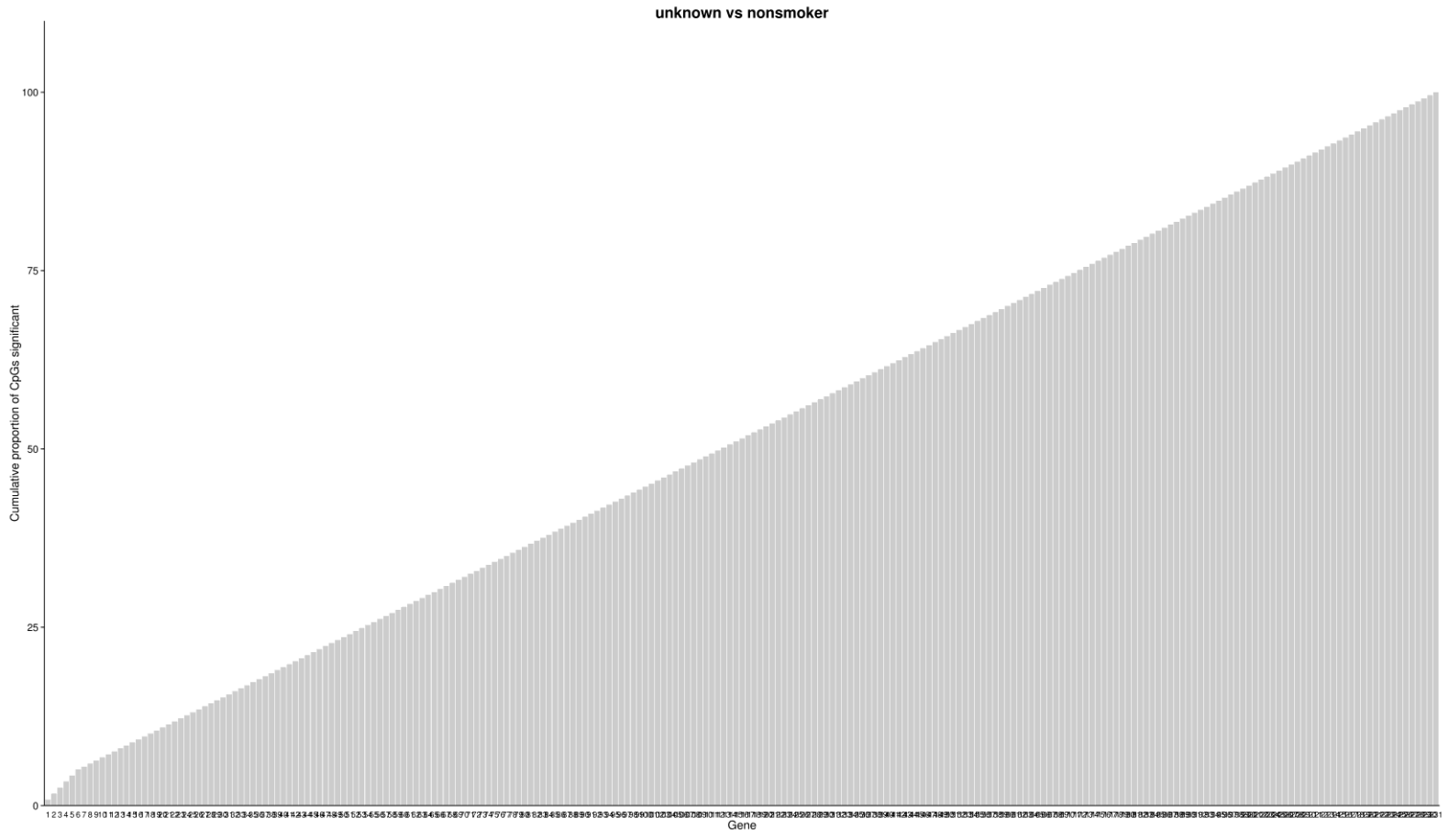
Smoking

- Use methylation data, current vs never smokers
- Take smallest p-value for each gene, 1/p re-normalise to generate a « probability of selection »
- AUC 98-99 %, 631 CPG sites FDR<0.05
- Q~1E-8

Significant CPG by gene



Unknown Smoking Status



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World Health Organization

Thanks

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